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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/337,756	06/22/1999	HANS J. HANSEN	018733/0884	9359

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EXAMINER	
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ART UNIT	PAPER NUMBER
1644	26

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
337,756	HANSEN et al
Examiner	**Group Art Unit**
SAUNDERS	1644

—The MAILING DATE of this communication appears on the cover sheet beneath the correspondence address—

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, such period shall, by default, expire SIX (6) MONTHS from the mailing date of this communication .
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).

Status

☑ Responsive to communication(s) filed on 3/17/03.

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle,* 1935 C.D. 1 1; 453 O.G. 213.

Disposition of Claims

☑ Claim(s) 1, 12-20, 30, 51-52 is/are pending in the application.

Of the above claim(s)_____ is/are withdrawn from consideration.

☐ Claim(s)_____ is/are allowed.

☑ Claim(s) 1, 12-20, 30, 51-52 is/are rejected.

☐ Claim(s)_____ is/are objected to.

☐ Claim(s)_____ are subject to restriction or election requirement.

Application Papers

☑ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The proposed drawing correction, filed on_____ is ☐ approved ☐ disapproved.

☐ The drawing(s) filed on_____ is/are objected to by the Examiner.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119 (a)-(d)

☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 11 9(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number)_____.

☐ received in this national stage application from the International Bureau (PCT Rule 1 7.2(a)).

*Certified copies not received:_____.

Attachment(s)

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s)._____

☑ Notice of Reference(s) Cited, PTO-892

☑ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Interview Summary, PTO-413

☐ Notice of Informal Patent Application, PTO-152

☐ Other_____

Office Action Summary

Claims 1, 12-20, 30, 51-52 and 55-56 are pending and under examination.

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 3/17/03 has been entered.

The following 112 rejections are newly stated:

Claims 1, 12-20, 30, 51-52 and 55-56 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In claims 1 and 30, parts (D)(1) through (D)(4) and in claims 51-52 "the target site" lacks antecedent basis. No "site" has been recited in parts (A)-(C).

Claims 16-19 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential structural cooperative relationships of elements, such omission amounting to a gap between the necessary structural connections. See MPEP § 2172.01. The omitted structural cooperative relationships are: the elements "peptide", "carbohydrate", "hapten" and "chelator" in claims 16-19 have no cooperative relationship with the elements recited in claim 1.

Specifically, one does not know whether or not these elements constitute the "epitope recognizable by said at least one other arm". If so, then applicant may consider overcoming by reciting these claims in the manner of claims 39-42 of copending application 09/382,186.

Claims 55 and 56 are unclear in relation to base claims 1 and 30. One has no idea what is meant by "when said first targetable conjugate additionally comprises a prodrug" because this "when" condition has never been recited as an alternative embodiment in claims 1 or 30. The first conjugate of the base claims has only been recited as comprising an enzyme. Further, the "second targetable conjugate" of claims 1 and 30 has a prodrug; there is thus confusion as to what constitutes the second conjugate.

Claims 55-56 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Claims 55-56 contain new matter.

Claims 55-56 have incorporated what was recited in original claims 2 and 31. Nevertheless, they contain new matter because base claims 1 and 30 have been amended from their original recitation wherein the first targetable conjugate" in part © generically comprises any conjugated" therapeutic or diagnostic agent" to their present recitation wherein the "first targetable conjugate" has been narrowed to an enzyme. While original claims 1 and 30 did allow for "one or more conjugated therapeutic or diagnostic agents" to be present in the "first targetable conjugate", the examiner nowhere finds any disclosure of providing the such a conjugate particularly having a combination of enzyme and prodrug agents.

Claims 55-56 rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to

which it pertains, or with which it is most nearly connected, to make and/or use the invention. One would not know how to practice the method of claim 55 in conjunction with the method of base claim 1. If one uses a "first targetable conjugate" which has both an "enzyme" (as required by claim 1 part (C)) and also a prodrug (as required by claim 55), how could one prevent the enzyme from activating the prodrug, when the "first targetable conjugate" is merely sitting in a vial? Note, that the prodrug moieties on any conjugate molecule would become activated, when such a molecule collides with another conjugate molecule. For this reason one would not know how to use the components provided in the kit of claim 56.

The following 112 rejections of record are repeated, since claim 20 was not canceled in the amendment of 3/17/03.

Claim 20 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 20 is unclear by reciting a "detectable radio nuclide", since base claim 1 refers to"treating" rather than "detecting". Claim 20 fails to set forth any functional relationship of the radio nuclide to the method of claim 1.

Claim 20 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Claim 20 contains new matter because the examiner cannot find where the

original disclosure specifically disclosed the use of a detectable radio nuclide on the bispecific antibody, in conjunction with the recited first (enzyme) and second (prodrug) conjugates-.

Claim 20 is rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific asserted utility or a well established utility.

Applicant's disclosure has not set forth the purpose for or utility of providing the recited detectable radio nuclide on the bispecific antibody.

Claim 20 is also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

Upon reconsideration of the prior art, the following new obviousness rejection is stated.

Claims 1, 12-16, 18-20, 30 and 51 are rejected under 35 U.S.C. 103(a) as being unpatentable over Barbet et al. or Goodwin et al., either in view of Bagshawe et al. (5,683,694).

Barbet et al. show bispecific antibodies with a first arm directed to a target to antigen on a cell and a second arm directed to a hapten component of a conjugate comprising one or more copies of the hapten and "effector" (i.e. therapeutic or diagnostic agent) group. The antibody arms in each case are taught as monoclonal (page 4, lines 50-65), in accord with instant claims 12-13.

The conjugates can contain peptide structures (page 5, lines 41-43) as in instant claim 16. In the case where the hapten of the conjugate is a metal-chelate (page 4, lines 38-55) the conjugate would be consistent with instant claim 19.

Barbet et al. teach a method in accord with instant claim 1 (page 6, lines 38-55) except for the facts that they do not specifically teach an enzyme as the therapeutic agent on the conjugate, and that they do not teach prodrugs.

Goodwin et al. show a method involving administration of a "binding protein", followed by a "clearing agent", followed by an "epitopic compound". See col. 10, line 10 - col. 12, line 10, for example. The "eptiopic compound" can include one or more hapten moieties, which are binding partners for an antibody, and which are linked to an therapeutically active agent or imaging agent. See col. 4, line 55 - col. 7, line 6. This "epitopic compound" corresponds to the targetable conjugate of instant claims 1 and 30, part C) of each. The "binding protein" can be comprised of monoclonal, bispecific antibodies, with one arm directed to a target tissue and a second arm directed to the epitopic compound. See col. 7, line 8 - col. 9, line 36, especially at col. 9, lines 3-36. This "binding protein" corresponds to the bispecific antibody of claims 1 and 30, part (A) of each.

Goodwin et al. teach the method of instant claim 1, except for the facts that the active agents contemplated by Goodwin et al. do not specifically include enzyme, and that prodrugs are not taught by Goodwin et al.

Bagshawe et al. show that it is known to employ bispecific antibodies, with one arm directed to a target antigen on a cell and a second arm directed to an enzyme, in a therapeutic method. The enzyme in such case converts a prodrug to an active drug at the site where the bispecific antibody has bound to antigen. See col. 2, lines 49-58.

Since Bagshawe et al. show that an enzyme that activates a prodrug is known to fall within the armamentarium of therapeutic agents that can be targeted by bispecific antibodies, it would have been obvious to provide the enzyme of Bagshawe et al. conjugated to a hapten/epitope recognized by the antibody in the second arm of the bispecific antibodies of Barbet et al. or Goodwin et al. The examiner considers that the lacks of teaching of prodrug activating enzymes as being among the therapeutic agents listed by Barbet et al. or Goodwin et al. Arise from the fact that prodrug activating enzymes were not well established as therapeutic agents at the time that Barbet et al. and Goodwin et al. filed, rather than from any consideration that such enzymes would not be compatible with their taught targeting methods.

The examiner considers that the combination of references is proper, since the cytotoxic drugs produced by the enzymes component of Bagshawe et al. correspond to the cytotoxic drugs taught by Barbet et al. (Page 5, lines 46-50). Further one would have fully expected that conjugates of hapten and enzyme would retain their prodrug activating function, because it has been conventional to provide conjugates of enzymes to other molecules, with a retention of enzymatic activity. See Bagshawe et al. at col. 2, lines 34-48 and at col. 7, line 56 - col. 8, line 59 regarding antibody - enzyme conjugates, for example.

Absent a showing on the record that the combination of references is improper, obviousness is properly stated. Bagshawe et al. are relied upon, also, for teaching humanized antibodies as conventional and as known for avoiding host immune responses against antibody (col. 2, line 59 - col. 3, line 42); as well as for teaching radiolabelling of a targeting conjugate (col. 6, lines 18-39). Thus limitations of instant clams 14-15 and 20 would have been obvious.

Regarding kit claim 30 none of the cited references teach a "kit" per se; however Goodwin et al. teach that it is known to provide the components required to conduct a method in the Form of a "system"; to the extent that a "kit" many may differ from a "system", perhaps in terms of packaging, such a feature would have been obvious for the sake of convenience.

Claims 16-17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Barbet et al. or Goodwin et al., either in view of Bagshawe et al. as applied to claim 1 above, and further in view of Wagner et al. (5,503,987).

Wagner et al. teach the further feature that small epitopic/haptenic moieties include "small peptides" and "saccharides" (col. 4, line 62) and that antibodies can be prepared against such. They further teach that bispecific antibodies having one arm directed against such moieties may be used in therapeutic treatments (col. 11, line 62 - col. 12, line 2). It thus would have been obvious that such epitopic/haptenic moieties would be employed in the conjugates recognized by the second arm of the bispecific antibodies used in the therapeutic methods of Barbet et al. or Goodwin et al.

Claim 52 is not rejected over this combination of references because the recited function of the enzyme component is not taught by the references.'

Claims 55-56 are not rejected because they are so confusing (112, second supra) that it is impossible to apply any art against these claims.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David A. Saunders, Ph.D., whose telephone number is (703) 308-3976. The examiner can normally be reached on Monday-Thursday from 8:00 a.m. to 5:30 p.m. The examiner can also be reached on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan, can be reached on (703) 308-3973. The fax phone number for the organization where this application or proceeding is assigned is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

D. Saunders:jmr

June 16, 2003

David A Saunders

DAVID SAUNDERS
PRIMARY EXAMINER
ART UNIT ~~182~~ 1644